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Declaration under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/018009 A1

(54) Title: A COMBINATION OF QUETIAPINE AND ZOLMITRIPTAN

(57) Abstract: The present invention relates to a combination comprising quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof, pharmaceutical compositions, processes for its preparation, the use thereof in the manufacture of a medicament and a method of treatment of disease and more particularly to a method of treatment of diseases typically treated with 5-HT $_{1D}$ agonists and/or atypical antipsychotics, in particularly, migraine, related conditions and for reducing or eliminating of migraine recurrence.

A COMBINATION OF QUETIAPINE AND ZOLMITRIPTAN

The present invention relates to a combination comprising the antipsychotic dopamine D2/5-HT_{2A} agent quetiapine or a pharmaceutically acceptable salt thereof and the 5-$HT_{1B/1D}$ agonist zolmitriptan or a pharmaceutically acceptable salt thereof, pharmaceutical compositions, processes for its preparation, the use thereof in the manufacture of a medicament and a method of treatment of disease and more particularly to a method of treatment of diseases typically treated with 5-$HT_{1B/1D}$ agonists and/or atypical antipsychotics. Such diseases include psychoses and related disorders, and migraine and related disorders. In particularly, migraine or related conditions, and for reducing or eliminating of migraine recurrence.

The co-administration of quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof leads to benefits over existing therapies.

Quetiapine has the chemical name 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4]thiazepine and is an antipsychotic agent that has been sold as the fumarate salt under the trademark Seroquel™ for a number of years. Quetiapine fumarate is marketed for the treatment of schizophrenia and related disease conditions. A considerable body of literature describes how to use quetiapine fumarate. Specific references for the preparation and use of this agent are EP 240228 and 282236, US 4,879,288 and WO 97/45124.

Zolmitriptan has the chemical name (S)-4-{{3-[2-(dimethylaminoethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone. Specific references for the preparation and use of this agent are EP 486666 and WO 97/06162. Zolmitriptan is a selective 5-$HT_{1B/1D}$-receptor agonist. During migraine excessive cerebrovascular dilation and neurogenic inflammatory processes are considered to contribute to pain. The 5-$HT_{1B/1D}$-receptors mediate cerebrovascular vasoconstriction and inhibit neurogenic inflammation. 5-$HT_{1B/1D}$ receptor agonists are beneficial in the treatment (including prophylaxis) of disease conditions wherein vasoconstriction and neurogenic inflammation in the cerbrovascular bed is indicated, for example migraine, cluster headache and headache associated with vascular disorders, hereinafter referred to collectively as migraine.

Zolmitriptan has been developed for the acute treatment of migraine in the form of a 2.5 mg and 5 mg tablet intended to be taken up to a maximum of 15 mg per day.

Although zolmitriptan is a successful drug of considerable benefit to migraine sufferers, there is a continuing need for alternative methods for the direct treatment of migraine and the prophylactic treatment of migraine and the treatment (direct and prophylactic) of related conditions.

The co-administration of quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof is expected to provide benefit in the treatment of migraine and related conditions for example the symptomatic treatment of pain relief, decreasing nausea, decreasing photophobia and phonophobia.

For example benefits may include greater efficacy where response to zolmitriptan alone is not as good as expected; greater efficacy (for example reduction in frequency and/or severity of episodes) against migraine attacks and their symptoms for example against persistent headache where recurrence is a problem and the rate of relapse needs to be reduced or eliminated including for example as part of a withdrawal regimen; where a migraine patient also suffers from psychoses, depression or anxiety; and a further benefit could be that lower doses of zolmitriptan may be given leading to greater tolerability and/or safety. In summary, the benefits may include increased number of patients that exhibit efficacy to zolmitriptan, increased number of patients that achieve pain-free status or near pain-free status, and decreased frequency of headache recurrence. Accordingly, the present invention provides a combination comprising quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof.

Other objects of the present invention provides a pharmaceutical composition comprising said combination, processes for the preparation of said combinations, a kit comprising said combination, optionally with instructions for use, and the use of said combination for the manufacture of a medicament for the treatment of migraine and related disorders, and for reduction or elimination of migraine recurrence.

A further object of the present invention provides a method of treating migraine or a related condition in a mammal which comprises administering to said mammal an amount of quetiapine or a pharmaceutically acceptable salt thereof and an amount of zolmitriptan or a pharmaceutically acceptable salt thereof so that the combination is effective in treating migraine or the related condition.

Another further object of the present invention provides a method of treating reduction or elimination of migraine recurrence in a mammal which comprises administering to said mammal an amount of quetiapine or a pharmaceutically acceptable salt thereof and an amount of zolmitriptan or a pharmaceutically acceptable salt thereof so that the combination is effective in treating reduction or elimination of migraine recurrence.

Quetiapine has demonstrated efficacy against agitation and anxiety; agitation and anxiety may contribute to the onset and persistence of migraine headaches leading to a further benefit of using quetiapine and zolmitriptan in combination.

Treating includes the direct and prophylactic treatment of migraine or related condition. Direct treatment includes elimination, reduction and alleviation of the disease and/or symptoms; prophylactic treatment includes preventative measures.

Migraine and related conditions include conditions wherein vasoconstriction in the carotid vascular bed is indicated; for example, migraine, cluster headache, headache associated with vascular disorders and aura.

Quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof may be administered in the same formulation (co-formulation) or separately, conveniently using marketed dosage forms and strengths.

The dosage form, dosage strength and frequency of dosing of zolmitriptan administered depends on various factors known in the art including the weight, age and sex of the patient being treated and the particular migraine disease condition being treated. Typically, a unit dose of about 0.5 mg to 15 mg (for example, 0.5 mg, 1.0 mg, 2.5 mg, 5.0 mg and 10 mg) of zolmitriptan is administered to the patient in need thereof. Zolmitriptan may be administered orally, intravenously, intranasally or by a fast-melt formulation that rapidly dissolves in the mouth. Typically, a daily dose for an adult human is in the range of about 0.5 mg to about 15 mg per day depending on the route of administration and the particular needs of the patient.

Formulations of zolmitriptan may be prepared according to EP 486666, WO 01/39772, US 5,178,878, US 6,024,981 and according to methods generally known in the art of formulation technology.

The dosage form, dosage strength and frequency of dosing of quetiapine administered also depends on the various factors known in the art including the weight, age and sex of the patient being treated. Typically, a unit dose of about 5 mg to 50 mg (for example, 5

mg, 10 mg, 25 mg and 40 mg) of quetiapine is administered to the patient in need thereof. Quetiapine may be administered parenterally or may be administered orally either in a conventional tablet or capsule or in a modified formulation such as a controlled, delayed or sustained release formulation.

Formulations of quetiapine may be prepared according to EP 240228 and according to methods generally known in the art of formulation technology. WO 01/21179 describes a formulation in the form of granules of quetiapine, which could be a further aspect of administration.

In a particular aspect, quetiapine or a pharmaceutically acceptable salt thereof is administered orally and zolmitriptan or a pharmaceutically acceptable salt thereof is administered orally or intranasally; preferably the drugs are administered orally, particularly the zolmitriptan is administered as a tablet or a fast melt formulation. Suitably zolmitriptan or a pharmaceutically acceptable salt thereof is administered in a 2.5mg or 5mg unit dose and quetiapine or a pharmaceutically acceptable salt thereof is administered in a 25mg unit dose.

In another particular aspect, quetiapine or a pharmaceutically acceptable salt thereof is administered in a controlled, delayed or sustained release dosage form. For example, dosage forms according to WO 97/45124 may be used. Such dosage forms provide a generally uniform and constant rate of release over an extended period of time to achieve a stable, desired blood (plasma) level of quetiapine without the need for frequent administration. This is particularly beneficial if the patient suffers from recurring migraine attacks as a stable level of quetiapine can be maintained.

In a particular aspect, the amount of zolmitriptan administered to a patient in need thereof can be lower than the amount of zolmitriptan that would be required if zolmitriptan were administered in the absence of quetiapine. Lower amounts of zolmitriptan may avoid side effects and/or improve tolerability in certain patients. In another particular aspect, the amount of quetiapine administered to a patient in need thereof can be lower than the amount of quetiapine that would be required if quetiapine were administered in the absence of zolmitriptan. Lower amounts of quetiapine may avoid side effects and/or improve tolerability in certain patients.

In another particular aspect, the administration of zolmitriptan and quetiapine can lead to greater and/or longer efficacy than would be the case in the absence of quetiapine.

In another aspect, quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof may be formulated in the same pharmaceutical composition with pharmaceutically acceptable carriers. Such a pharmaceutical composition may be administered orally (e.g. tablets, capsules) or by injection (e.g. a solution). Such compositions may be prepared in a conventional manner with suitable pharmaceutically acceptable carriers such as binding agents, fillers, disintegrates and solubilizing agents.

There are currently no animal models of migraine that are considered to be completely predictive of efficacy in humans. However, animal models are available that are considered to mimic important aspects of migraine pathophysiology. The injection of lipopolysaccharides (LPS) into the cerebral ventricles of rats causes cerebral inflammation, an inflammatory process that may occur in migraine. Directing an air puff to the head of the rat and measuring ultrasonic vocalizations can assess the pain resulting from this process. This method is described in detail below:

i) Administration of LPS

Rats are allowed to habituate in the experimental laboratory for 15-20 minutes prior to treatment. Cerebral inflammation is induced by administration of LPS (endotoxin of gram-negative *E. coli* bacteria serotype 0111:B4, Sigma). LPS (2.4μg) is injected intracerebro-ventricularly (i.c.v.), in a volume of 10μl, using standard stereotaxic surgical techniques under isoflurane anesthesia. The skin between the ears is pushed rostrally and a longitudinal incision of about 1cm is made to expose the skull surface. The puncture site is determined by the coordinates: 0.8 mm posterior to the bregma, 1.5 mm lateral (left) to the lambda (sagittal suture), and 5 mm below the surface of the skull (vertical) in the lateral ventricle. LPS is injected via a sterile stainless steel needle (26-G 3/8) of 5 mm long attached to a 100-μl Hamilton syringe by polyethylene tubing (PE20; 10-15 cm). A 4 mm stopper made from a cut needle (20-G) is placed over and secured to the 26-G needle by silicone glue to create the desired 5mm depth.

Following the injection of LPS, the needle remains in place for an additional 10 seconds to allow diffusion of LPS, then is removed. The incision is closed, and the rat is returned to its original cage and is allowed to rest for a minimum of 3.5 hours prior to testing.

ii) Experimental setup for air-puff stimulation

The rats remain in the experimental laboratory following LPS injection and drug administration. At the time of testing all rats are removed and placed outside the laboratory. One rat at a time is brought into the testing laboratory and placed in a clear box ($9 \times 9 \times 18$ cm) which is then placed in a sound-attenuating ventilated cubicle measuring 62(w) ×35(d) ×46(h) cm (BRS/LVE, Div. Tech-Serv Inc). Air-puffs are delivered, through an air output nozzle of 0.32 cm, which is controlled by a system (AirStim, San Diego Instruments) capable of delivering puffs of air of fixed duration (0.2 s) and fixed intensity with a frequency of 1 puff per 10 seconds. A maximum of 10 puffs are administered, or until vocalization starts, which ever comes first. The first air puff marks the start of recording.

iii) Experimental setup for and ultrasound recording

The vocalizations are recorded for 10 minutes using microphones (G.R.A.S. sound and vibrations, Vedbaek, Denmark) placed inside each cubicle and controlled by LMS (LMS CADA-X 3.5B, Data Acquisition Monitor, Troy, Michigan) software. The frequencies between 0 and 32000Hz are recorded, saved and analyzed by the same software (LMS CADA-X 3.5B, Time Data Processing Monitor and UPA (User Programming and Analysis)). The number of ultrasonic vocalizations induced by air puffs is taken as a measure of pain experienced by the rats.

iv) Analysis

The recordings are run through a series of statistical and Fourier analyses to filter (between 20-24kHz) and to calculate the parameters of interest. The data are expressed as the mean ± SEM. Statistical significance are assessed using T-test for comparison between naive and LPS-treated rats, and one way ANOVA followed by Dunnett's multiple comparison test (post-hoc) for drug effectiveness. A difference between groups is considered significant with a minimum p value of ≤ 0.05. Experiments are repeated a minimum of two times.

Examples

1) An adult patient experiencing the onset of migraine is treated with quetiapine fumarate (25 mg) and zolmitriptan (5 mg). Quetiapine fumarate is administered as a tablet ('Seroquel') and zolmitriptan is also administered as a tablet ('Zomig').

2) A tablet is prepared as follows:

	mg
Quetiapine Fumarate	28
Zolmitriptan	5
Povidone	7.00
Calcium Hydrogen Phosphate	8.72
Microcrystalline cellulose	28.50
Lactose monohydrate	19.00
Sodium starch glycollate	7.00
Magnesium stearate	1.00
Coating	
Methylhydroxypropylcellulose	1.56
Macrogel 400	0.31
Titanium dioxide	0.59
Ferric oxide, red	0.02
Ferric oxide, yellow	0.02

The ingredients are mixed with purified water, blended and compressed into tablets, which are then coated.

CLAIMS

1. A combination comprising quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof.

2. A combination according to claim 1 for use simultaneously, sequentially or separately as a medicament.

3. A combination according to claim 1 for use simultaneously, sequentially or separately for the treatment of migraine or related conditions.

4. A combination according to claim 1 for use simultaneously, sequentially or separately for reducing or eliminating of migraine recurrence.

5. A combination according to anyone of claims 1-4 wherein quetiapine or a pharmaceutically acceptable salt thereof is administered orally and zolmitriptan or a pharmaceutically acceptable salt thereof is administered orally or intranasally.

6. A combination according to any one of claim 5 wherein quetiapine or a pharmaceutically acceptable salt thereof is administered orally and zolmitriptan or a pharmaceutically acceptable salt thereof is administered orally.

7. A combination according to claim 6 wherein quetiapine or a pharmaceutically acceptable salt thereof is administered as a tablet and zolmitriptan or a pharmaceutically acceptable salt thereof is administered as a tablet.

8. A combination according to anyone of claims 1-7 wherein zolmitriptan or a pharmaceutically acceptable salt thereof is administered as a fast melt formulation.

9. A combination according to any one of claims 1-7 wherein quetiapine or a pharmaceutically acceptable salt thereof is administered in a controlled delayed or sustained release dosage form.

10. A combination according to any one of claims 1-9 wherein zolmitriptan or a pharmaceutically acceptable salt thereof is administered in a unit dose of about 0.5 to15 mg and quetiapine or a pharmaceutically acceptable salt thereof is administered in a unit dose of about 5 to 50 mg.

11. A combination according to claim 10 wherein zolmitriptan or a pharmaceutically acceptable salt thereof is administered in a 5 mg unit dose and quetiapine or a pharmaceutically acceptable salt thereof is administered in a 25 mg unit dose.

12. A combination according to any one of claims 1-11 wherein the quetiapine pharmaceutically acceptable salt is quetiapine fumarate.

13. A combination according to any one of claims 1-12 comprising zolmitriptan and quetiapine fumarate.

14. A pharmaceutical composition comprising the combination according to any one of claims 1-13 and optionally a pharmaceutical carrier or diluent.

15. A pharmaceutical composition according to claim 14 for use simultaneously, sequentially or separately as a medicament.

16. A pharmaceutical composition according to claim 15 for use simultaneously, sequentially or separately in the treatment of migraine or related conditions.

17. A first pharmaceutical composition comprising quetiapine or a pharmaceutically acceptable salt thereof and optionally a pharmaceutical carrier or diluent and a second pharmaceutical composition comprising zolmitriptan or a pharmaceutically acceptable salt thereof and optionally a pharmaceutical carrier or diluent.

18. Use of a combination according to any one of claims 1-17 for the manufacture of a medicament for administration simultaneously, sequentially or separately to a mammal for the treatment of migraine or related conditions.

19. Use of a combination according to any one of claims 1-17 for the manufacture of a medicament for administration simultaneously, sequentially or separately to a mammal for reducing or eliminating of migraine recurrence.

20. A method for lowering the unit dose of zolmitriptan or a pharmaceutically acceptable salt thereof by administration of a combination according to any one of claims 1-17.

21. A method for reducing the frequency and/or severity of episodes of migraine attacks and their symptoms by administration of a combination according to any one of claims 1-17.

22. A method for reducing or eliminating of migraine recurrence by administration of a combination according to any one of claims 1-17.

23. A method for improving the efficacy of zolmitriptan or a pharmaceutically acceptable salt thereof by using quetiapine or a pharmaceutically acceptable salt thereof.

24. A method of treating migraine or a related condition in a mammal that comprises administering to said mammal an amount of quetiapine or a pharmaceutically acceptable salt thereof and an amount of zolmitriptan or a pharmaceutically acceptable salt thereof.

25. A method according to claim 24 wherein the quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof are administered simultaneously, sequentially or separately.

26. A method according to any one of claims 20-24 wherein quetiapine or a pharmaceutically acceptable salt thereof is administered orally and zolmitriptan or a pharmaceutically acceptable salt thereof is administered orally or intranasally.

27. A method according to any one of claim 26 wherein quetiapine or a pharmaceutically acceptable salt thereof is administered orally and zolmitriptan or a pharmaceutically acceptable salt thereof is administered orally.

28. A method according to claim 27 wherein quetiapine or a pharmaceutically acceptable salt thereof is administered as a tablet and zolmitriptan or a pharmaceutically acceptable salt thereof is administered as a tablet.

29. A method according to anyone of claims 20-28 wherein zolmitriptan or a pharmaceutically acceptable salt thereof is administered as a fast melt formulation.

30. A method according to any one of claims 20-28 wherein quetiapine or a pharmaceutically acceptable salt thereof is administered in a controlled, delayed or sustained release dosage form.

31. A method according to any one of claims 20-30 wherein zolmitriptan or a pharmaceutically acceptable salt thereof is administered in a unit dose of about 0.5 to15 mg unit dose and quetiapine or a pharmaceutically acceptable salt thereof is administered in a unit dose of about 5 to 50 mg unit dose.

32. A method according to claim 31 wherein zolmitriptan or a pharmaceutically acceptable salt thereof is administered in a 5 mg unit dose and quetiapine or a pharmaceutically acceptable salt thereof is administered in a 25 mg unit dose.

33. A process for the preparation of a combination according to any one of claims 1- 16 wherein quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan

or a pharmaceutically acceptable salt thereof are incorporated in the same pharmaceutical composition.

34. A process for the preparation of a combination according to any one of claims 1-17 wherein quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof are in different pharmaceutical composition.

35. A kit comprising quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof, optionally with instructions and/or labeling for the use.

36. The kit according to claim 35 wherein quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof are for simultaneous or contemporaneous administration.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01507

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/422, A61K 31/4045, A61K 31/55, A61P 25/06, A61P 25/18
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 9745124 A1 (ZENECA LIMTED), 4 December 1997 (04.12.97), page 13, line 21 - page 14, line 5, the claims --	1-36
Y	WO 0121179 A1 (ASTRAZENECA AB), 29 March 2001 (29.03.01), page 6, line 14 - line 19, the examples --	1-36
Y	STN International, File CAPLUS, CAPLUS accession no. 1998:130310, document no. 128:225529, Caley, Charles F. et al: "Focus on quetiapine: the fourth atypical antipsychotic";& Formulary (1998), 33(2),105-106,109-110,112, 115-116,119 --	1-36

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 October 2002	06-11-2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer GERD STRANDELL/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01507

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Phychopharmacology, Volume 140, No. 4, 1998, A.J. Mecer et al: "Lack of an effect of zolmitriptan (Zomig, 311C90)on psychometric task performance: results of a placebo-controlled study in healthy volunteers", pages 398-404 --	1-36
Y	WO 0139772 A1 (ASTRAZENECA AB), 7 June 2001 (07.06.01) --	1-36
Y	WO 9735584 A1 (ELI LILLY AND COMPANY), 2 October 1997 (02.10.97), page 7, line 19 - line 27; page 13, line 18 - line 22, the claims --	1-36
Y	GB 2324961 A (MERCK SHARP & DOHME LIMITED), 11 November 1998 (11.11.98), page 2, line 22 - line 23; page 5, line 13 - line 18, the claims -- --------	1-36

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 20-32
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/01507

Claims 20-32 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule. 39.1.(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/09/02

International application No.
PCT/SE 02/01507

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9745124 A1	04/12/97	AT 222105 T	15/08/02
		AU 727219 B	07/12/00
		AU 2967597 A	05/01/98
		BR 9709271 A	10/08/99
		CA 2251944 A	04/12/97
		CN 1219879 A	16/06/99
		CZ 9803880 A	17/02/99
		DE 69714739 D	00/00/00
		EP 0907364 A,B	14/04/99
		GB 9611328 D	00/00/00
		GB 9709761 D	00/00/00
		HR 970299 A,B	30/04/98
		IL 127222 A	19/03/01
		JP 2000511170 T	29/08/00
		KR 2000011013 A	25/02/00
		NO 985539 A	27/11/98
		NZ 332198 A	26/05/00
		PL 330223 A	10/05/99
		SK 163998 A	07/05/99
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